FEBS Letters 589 (2015) 2958–2965

FEBS Letters

journal homepage: www.FEBSLetters.org

Review

The role of loops on the order of eukaryotes and prokaryotes

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ARTICLE INFO

Article history:
Received 28 February 2015
Revised 14 April 2015
Accepted 14 April 2015
Available online 23 April 2015

Edited by Wilhelm Just

Keywords:
Polymer modeling
Topological domain
Chromatin looping

ABSTRACT

The study of the three-dimensional organization of chromatin has recently gained much focus in the context of novel techniques for detecting genome-wide contacts using next-generation sequencing. These chromosome conformation capture-based methods give a deep topological insight into the architecture of the genome inside the nucleus. Several recent studies observe a compartmentalization of chromatin interactions into spatially confined domains. This structural feature of interphase chromosomes is not only supported by conventional studies assessing the interaction data of millions of cells, but also by analysis on the level of a single cell. We first present and examine the different models that have been proposed to elucidate these topological domains in eukaryotes. Then we show that a model which relies on the dynamic formation of loops within domains can account for the experimentally observed contact maps. Interestingly, the topological domain structure is not only found in mammalian genomes, but also in bacterial chromosomes.

1. Introduction

Mammalian interphase chromosomes are hierarchically organized [1,2]. On the one hand, at the level of the nucleus, fluorescence in situ hybridization (FISH) and genome-wide chromosome conformation capture (3C) studies, such as Hi-C, have revealed an inter-chromosomal compartmentalization in the form of the formation of distinct chromosome territories [3,4]. Individual chromosomes, on the other hand, also show a domain-like structure as observed in recent genome-wide high-resolution Hi-C and 5C studies [5–7]. These 3C-like studies indicate that eukaryotic genomes are partitioned, at the sub-megabase level, into discrete structural units with highly increased frequency of internal contacts, referred to under different terms, such as "topological domains" [5], "topologically associating domains" (TADs) [6] and "physical domains" [7]. We will stick to the term "topological domains" for these intra-chromosomal domains, within which the chromatin fiber preferentially interacts. This finding of a domain organization of individual chromosomes is not only supported by data stemming from 3C-like studies examining genomic interactions of a large population of cells, but also by an analysis of individual cells, the single-cell Hi-C methodology [8].

Besides the eukaryotic chromosomes of humans, mice and *Drosophila melanogaster*, bacterial chromosomes are also characterized by a hierarchical organization [9]. The *Escherichia coli* chromosome consists of macrodomains on the megabase scale [10,11], which, in turn, are composed of topological domains on the smaller scale [12]. Recently, the circular chromosome of Caulobacter crescentus, as a further example, has been shown to be composed of topological domains with the help of an in-depth Hi-C analysis [13]. Taken together, these analogies to the organization in eukaryotes suggest that an intra-chromosomal domain structure is a fundamental building block of chromosome structure of organisms.

Although their important role in shaping the three-dimensional organization of the genome seems acknowledged, there remains the question how topological domains are established, hence what causes the increased contact frequency within these genomic regions. One striking observation is that most identified enhancer–promoter pairs have been shown to belong to the same topological domain [14,15]. The finding that these enhancer–promoter units mostly coincide with topological domains [14], however, has to be treated with caution since the increased background of the interactions within topological domains was not taken into consideration in this analysis.

As enhancer–promoter activity is known to involve DNA loop formation [16–18] this hints at an important organizational role of loops [19–21]. In fact, there is emerging evidence that loops contribute to compartmentalization in the eukaryotic genome

Author contributions: Conceived and designed the experiments: AH DWH. Performed the experiments: AH. Analyzed the data: AH. Wrote the paper: AH DWH.

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http://dx.doi.org/10.1016/j.febslet.2015.04.021

[18] and that a fraction of topological domains actually corresponds to loop domains that are conserved across cell types as well as species and stable against cell-to-cell variation [18]. Looped structures are thereby likely to be made up of both dynamic looping interactions [22] and a network of static loops [18]. The presence of these loops creates entropic constraints that helps maintaining chromosome structure. The role of proteins that are involved in the formation of loops, such as CTCF and cohesin, is complex, but has been established through 3C-related and chromatin immunoprecipitation studies [23,24] as well as FISH experiments [25]. However, it is controversial whether the two proteins are also involved in establishing topological domains [26,27].

In this review, we shed light on the theoretical analysis of topological domains appearing as a ubiquitous feature in contact maps based on current high-resolution Hi-C data. After the presentation of modeling approaches that appeared in the literature so far and aim to explain the appearance of topological domains, we investigate a model that is based on chromatin looping and incorporates the concept of topological domains. We conclude with a summary of the effects that loops have on the nuclear organization not only in mammalian genomes, but also in the bacterial nucleoid.

2. Current state of modeling

Although topological domains have been repeatedly discovered in current high-resolution chromosome conformation capture experiments [5–7] as well as earlier [28] and this substructure seems to be an essential characteristics of interphase chromosomes, only little is known about their internal structure and organization. Several models have been proposed to theoretically explain the observed clusters of increased contact frequency in contact maps, none of which accounts for the essential role of loops.

The model of Benedetti et al. [29] is designed to reflect the situation where unconstrained supercoiling, referring to the over- or under-winding of the DNA double strand, acts on chromatin fibers that are sparsely attached at specific sites to nuclear granules. This model is supported by reports indicating that boundary elements of topological domains are attached to nuclear granules and, more importantly, reports indicating that chromatin fibers are supercoiled [30]. In this proposed model, individual topological domains are simulated as polymer rings. The closure is thereby essentially needed for maintaining the torsional tension introduced in order to be able to get (super-) coiled structures. Without an actual closure of the polymer chain possible torsional tension would be released through free rotation of the ends, thus a modeling of supercoiling would not be possible. However, this strategy of preventing the untangling problem comes with the price that actually one half of those supercoiled rings has to be neglected in the statistics of contacts. Additionally to the torsional potential for the purpose of introducing supercoiling into the model, it incorporates excluded volume interactions between monomeric beads as well as a bond length and a harmonic bending potential. For mimicking the effect of high concentration of chromatin in the eukaryotic nucleus, i.e. an increased contact probability of the polymer chain, Benedetti et al. performed their simulations in cubic confinement such that the simulated chains occupied 20% of the available volume. Simulated plectonemes appear in the average contact maps of simulated chromatin fragments as compartments of increased contact frequency, thus resembling the experimental contact maps. The underlying principle of the separation of individual domains or plectonemes in this modeling approach simply follows entropic repulsion, namely, the permanently connected polymer rings repel each other, such that fixed boundaries between supercoiled regions, i.e. topological domains, arise. The supercoiling of individual rings strengthens entropic repulsion.

The idea of the "strings and binders switch" (SBS) model proposed by Barbieri et al. [31,32] is to allow for the attachment of diffusible factors (binders) to binding sites along the simulated polymer chain. The obtained polymer configurations are thus dependent on binding site distribution, binder concentration and binding affinity. The polymer fiber itself is modeled as self-avoiding polymer bead chain and the binding molecules are represented by Brownian particles with a certain concentration. A fraction of polymer sites can be bound by diffusing molecules with a certain chemical affinity. Molecules binding to more than one polymer site lead to the formation of loops. To explore the formation of chromatin globules in the SBS model, Barbieri et al. assumed a polymer containing different kinds of binding sites, i.e. specialized binding sites, each with specific affinity to one kind of binder. As a consequence, each topological domain corresponds to one specific binder. Under these conditions, the SBS model produces separate domains of increased contact frequency, though it is important to notice that the contact frequency in the appearing domains does not monotonically decrease with increasing distance from the main diagonal. This characteristic of the contact map averaging over the ensemble of simulated polymer configurations indicates that the domains are rather stiff.

In the same light of the SBS model, it was recently observed that regularly-spaced bridging in combination with a homogeneous self-adhesion interaction along a linear polymer chain can lead to a stable multi-domain configuration, hence a compartmentalization into topological domains [33].

3. Static loop domains

Inspired by the observation of thousands of loops both in a very recent high-resolution in situ Hi-C study of the human genome [18] and in earlier studies [34,35], we analyze the connection between loops and topological domains. These loops were found to link promoters and enhancers, correlate with gene activation and are conserved across cell types and species. Furthermore, it is observed that they are formed at domain boundaries and bind CTCF.

While the resolution of the Hi-C contact maps discussed in connection with the observations of topologically associating domains [5,6] is sufficient to show the existence of these distinctive clusters of high contact frequency, it does not allow for the analysis of their intrinsic structure. It was only with the high-resolution in situ Hi-C study of Rao et al. [18] that certain ends of individual topological domains were detected to be attached to each other forming simple loops or some kind of network of loops. Since loops are observed to demarcate a fraction of the boundaries of topological domains [18], we follow the terminology of Rao et al. and refer to such domains as "loop domains". Being interested in the composition of contact maps of such loop domains, we modeled systems composed of one and two static loops (see Fig. 1A and B) to see whether they resemble the structures in the experimental Hi-C data. As depicted by means of the contact maps in Fig. 1, the presence of simple loops results in formation of sharply defined squares in the contact map showing high intensity of contacts around their vertexes that are distal from the diagonal. These prominent peaks in the contact map reflect the fact that the border elements belonging to the same topological domains were brought together by the loop closure. The contact map of the polymer system composed of two loops of different size illustrates that neighboring loops do not interact due to entropic repulsion; a finding that has been quantified for ring polymers [36]. This feature becomes even clearer if we look at the contact probability profiles,

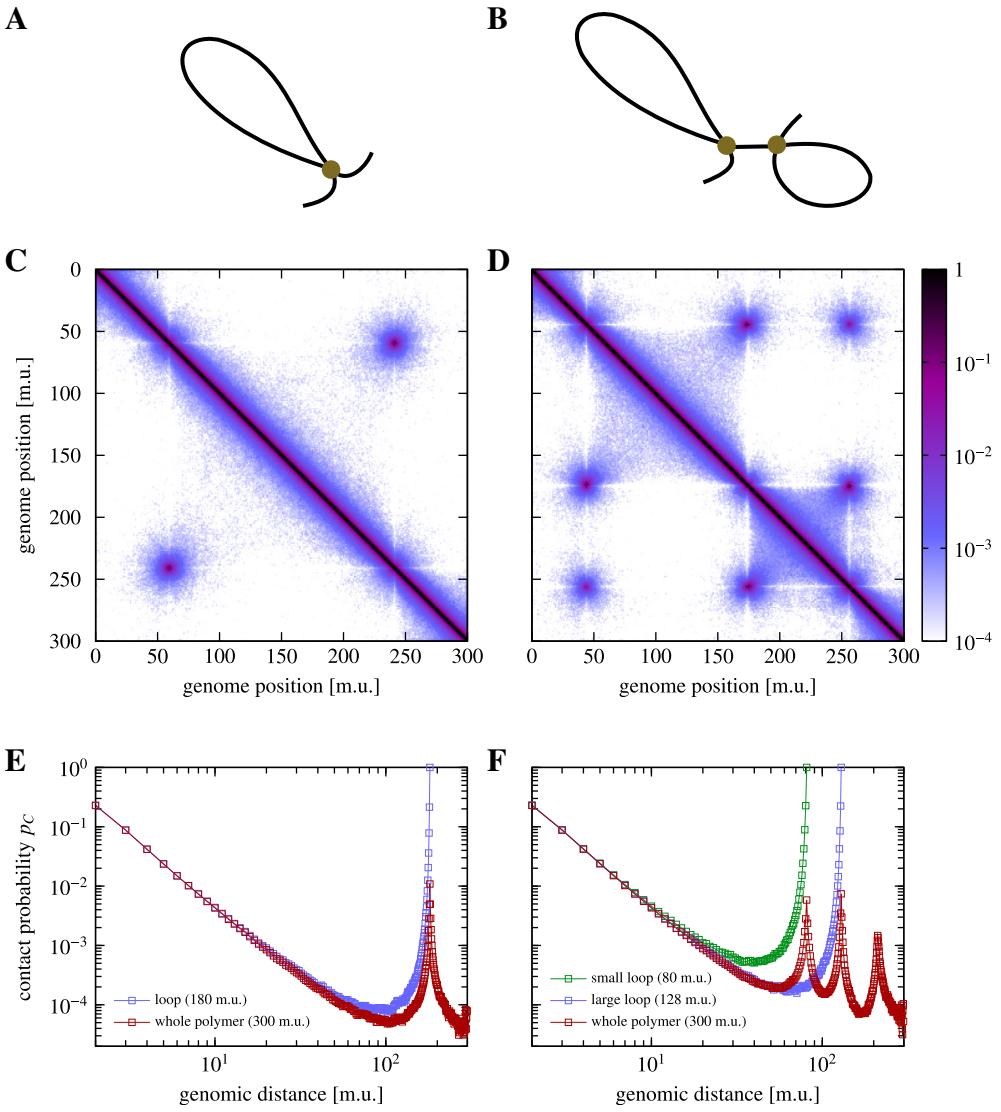

Fig. 1. Simple loop models recapitulate the experimental observation of "loop domains". (A and B) Sketches of the loop topologies for our polymer simulations. (C) Contact map for a simulated polymer comprised of a single static loop. The polymer ($N = 300$ monomers) is composed of a static loop modeling a topological domain with a size of $N = 180$ monomer units (m.u.). (D) Contact map for a simulated polymer comprised of two single static loops. The polymer ($N = 300$ monomers) is composed of two static loops modeling two topological domains with sizes of $N = \{128, 80\}$ monomers, respectively. (E and F) The contact probability profile of both polymer topologies is shown for both the individual domains (loops) and the whole conformations, respectively. The loop closures generate local maximums in the graph showing the genome-wide profile.

i.e. contact probability as a function of the genomic distance (see Fig. 1E and F). Initially the probability of genome-wide contacts decreases with separating genomic distance. However, as this distance exceeds half of the total loop size, we observe an actual increase of the contact probability reaching a maximum at a distance that equals the loop size. The resulting "U" shape of the contact probability profiles of both individual domains and the whole polymer is due to the fact that genomic distant regions close to two border elements of the same domain are brought together by the loop closure. In fact, this prominent shape is a distinctive feature between contact probability profiles of loop domains and those of topological domains as observed in [5,6] since the latter monotonously decrease with increasing genomic distance.

4. Dynamic loop interaction within domains

Regardless of the evidence for invariable DNA loop domains throughout the genome, the question remains on which structural principle topological domains are based. Certainly, these domains that show a strict decrease in contact probability as a function of increasing intra-domain genomic distance rather than a peaked contact probability at the corner do not correspond to invariable loops. It is, however, possible to think of these domains in terms of simple loops forming only for a certain fraction of time and stay open for the rest. Moreover, we have to bear in mind that the experimental Hi-C data are derived from a large population of cells. Hence, we deal with contact information stemming from an ensemble of cells with possible conflicting conformations on average.

Based on these considerations, it is obvious to think of loops in a dynamic fashion. Topological domains may be established through a dynamic looping mechanism as sketched in Fig. 2. This schematic is based on the idea that distant regulatory elements make direct contact with either the promoter or another regulatory element of the gene they control, i.e. form a loop. As indicated in the introduction, such enhancer–promoter interactions are particularly frequent within topological domains [14]. The coincidence of enhancer–promoter units with topological domains suggests that

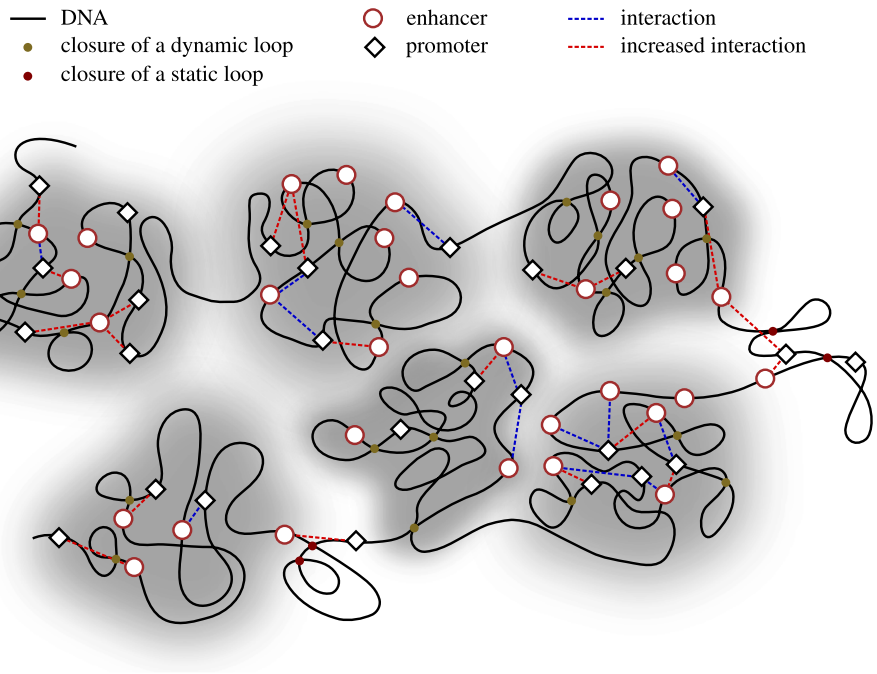

Fig. 2. Schematic illustration of both the dynamic loop interaction within intrachromosomal domains and static loops. Promoters (black) and enhancers (red) are represented by diamonds and circles. Interactions relevant to gene expression are shown as dotted lines. Dashed red lines thereby indicate interactions enhanced by a loop as opposed to dashed blue lines that represent interactions not enhanced by a loop. Loop closures caused by certain linking proteins as well as enhancer–promoter interaction are shown as small filled circles and can be both temporary (gold-colored) and static (ruby-colored). A snapshot of the three-dimensional organization of the genome is depicted with the interactions between genomic elements. The spatial organization and the loop topology is partly subject to fluctuations that affect gene expression. However, this dynamics does not lead to a change in the organization of topological domains (shadowed areas).

a dynamic loop domain structure underlies the topological domain structure. Analogously, loops could also dynamically form within loop domains.

A recent simulation study [37] analyzes how the looping interaction between elements in the vicinity of an enhancer–promoter pair influences their contact frequency. The simulations show that a chromatin loop, formed by elements flanking either an enhancer or a promoter, suppresses enhancer–promoter interaction, working as an insulator. In contrast, a loop formed by elements located in the region between an enhancer and a promoter, facilitates their interaction. Many enhancers, promoters, and loop-forming elements are present in a given genomic region (see Fig. 2), leading to a complex network of insulation and facilitation processes. Facilitation results from the effectively shortened genomic distance between enhancer and promoter due to the loop. Insulation is due to excluded volume interaction and steric exclusion by the loop. Taken altogether, loop topology influences promoter-enhancer interaction and vice versa (as depicted in Fig. 2).

We model these effects altogether by a dynamic and probabilistic loop formation within topological domains. To this end, we use a simple polymer model that has already been shown to explain the formation of distinct chromosome territories. In this dynamic loop (DL) model, the chromosomal fiber is represented as a self-avoiding (SAW) random walk polymer allowed to form probabilistic intra-polymer crosslinks between non-adjacent monomers [21]. As a consequence, loops of different size are formed. The main model parameter is the looping probability (p_{loop}), a measure for the probability that a loop is formed between two non-adjacent monomers. The dynamic formation and dissolution of loops thereby mimics the highly dynamic nature of enhancer–promoter loops as well as cell-to-cell variation that also supports variations in the loop topology. The simple example conformation is only consisting of two domains of different size as we are interested in the qualitative effects of dynamic looping on the contact probability measures rather than fitting our model to available experimental datasets. The results for the contact map and the contact probability profile are shown in Fig. 3 and could be fitted to those observed experimentally as it is possible to adjust the looping frequency and thus contact probability for individual domains. Moreover, by restricting the loop interaction to regularly spaced sites along the polymer chain as well as confining the interaction to certain compartments, our model adapts to the specificity binder model discussed previously. In fact, the SBS model, which assumes a diffusible component being responsible for loop formation by linking two monomers of the polymer, is a special case of the DL model implicitly incorporating the properties of such binders in the looping probability parameter much like the implicit water in the interaction potentials that are derived for proteins.

5. Effect of loops on the nuclear organization

Specifically in human cells the zinc finger protein CTCF and the protein complex cohesin have been linked to the formation and maintenance of loops. CTCF has even been named the master weaver of the genome [23,26,27,38,39]. Surprisingly, however, little is known about the interaction of these proteins with DNA [40,41].

In bacteria, nucleoid-associated proteins, such as H-NS, HU, Fis and IHF, can influence DNA structure locally by bending and wrapping DNA segments [42] as well as globally by looping [43,44] and by providing boundaries for DNA topological domains [45]. A recent approach investigating the spatial distribution of H-NS in *E. coli* using both super-resolution microscopy and 3C provides evidence for the juxtaposition of distant DNA segments interacting with H-NS [46].

Because of their implications in the formation of loops, experiments have interfered with cohesin and CTCF as well as the zinc-finger protein family in general [27,47,48]. Contrary to expectation, a recent FISH study [25] shows that the chromosomes do not swell

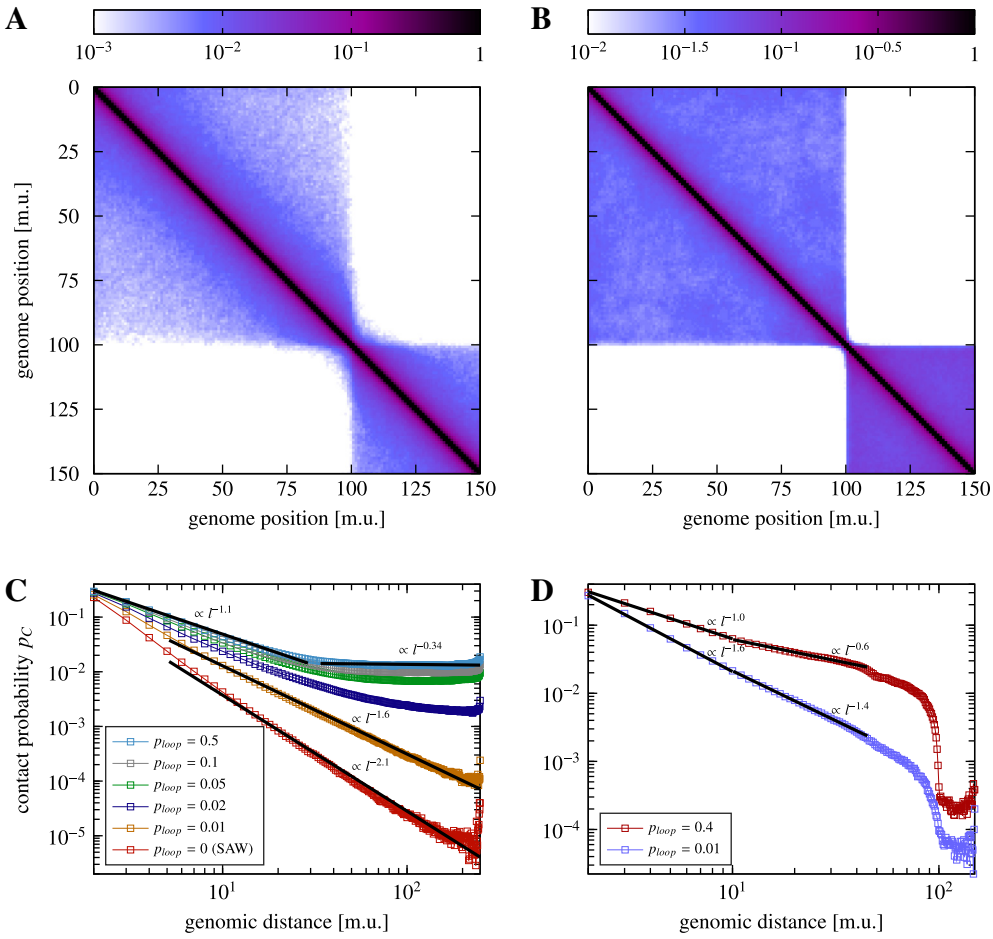

Fig. 3. (A and B) Contact maps of simulated polymers ($N = 150$ monomers) composed of two domains with varyingly strong dynamic looping ($p_{loop,A} = 0.01, p_{loop,B} = 0.4$) resemble those of experimentally observed topological domains. (C) The contact probability p_c for two specific sites as a function of the genomic separation between them. Shown are the results for equilibrated polymers composed of $N = 250$ monomers and various looping probabilities including the case of the self-avoiding walk ($p = 0$) and a simple random walk. The contact probability decreases as a power-law $l^{-\beta}$ with genomic separation for separations $n \gtrsim 10$. As already discussed by Bohn et al. [21], the exponent is thereby strictly dependent on the looping probability. Compared to the self-avoiding walk, the co-localization probability is strongly increasing due to dynamic looping. (D) The contact probability profiles for both polymers strictly decrease as a function of the genomic distance. The two functions can be partitioned into two regimes ($2 \leqslant l \leq 10, 10 \leqslant l \leq 45$) where their decrease can be approximated by power laws as depicted in the graph.

but compactify as a consequence of the depletion of these two proteins and hence a decline of loops. This observation is quite puzzling since loops are coupled with an increased level of compaction and provide a consistent framework [19,21] for the explanation of various experiments, such as Hi-C [49,4] as well as FISH experiments [50].

Moreover, the segregation of domains, and thus also the TADs within one chromosome can be explained within the loop framework [51,2]. Also in *E. coli* [52–54] the segregation of chromosomes can be explained.

At least three factors influence this segregation. First, there is the repulsion between the loops [21,55]. Indeed this is due to the entropic repulsion between the loops, i.e., based on the excluded volume of the monomers. Here entropy enters as an ordering mechanism which is a very interesting phenomenon [56–58] since with entropy one usually associates disorder. The solution to this puzzle is the change in topology in the chromosome as viewed as a polymer. Since *E. coli* is per se a circular chromosome upon replication the two chromosomes will separate [59].

Essentially due to repulsion between the loops there is a segregation between the more compact loops and those which are less compact. One can think of this as corresponding to heterochromatin and euchromatin. This segregation can be linked to the expression level of the chromosome such that those regions with high expression correspond to the not so compact loops and those with low expression to those regions with little expression [60]. Thus the chromosome is made up of domains of varying degree of loops in size and compaction.

Second, in confined space this would also be true for linear chromosomes as has been shown very convincingly by Jun and Mulder [61], at least the fact that the two linear chromosomes separate, not necessarily the internal segregation. However, what maintains the separation to a very high degree? Even though the chromosomes will separate, there is nevertheless almost always an overlap between the two chromosomes. To assist in helping and maintaining the separation the MinD proteins have been shown to play a crucial role [62].

Even on the level of the nucleus this ordering (loops that repel each other, leading to the formation of domains within the chromosome) holds true. The segregation of chromosomes in the human nucleus [3] can be explained in the framework of loops [21]. Since chromosomes in this picture are made up of loop domains within loop domains which themselves are loops clearly they repel each other. As a matter of fact the force that each chromosome exerts onto the other can be calculated [21]. Rosa and Everaers [63] have argued on the basis of classical polymer theory that linear polymers do not mix due to the long relaxation. The point of view taken here is that the polymer is much shorter due

to the loops and that the entire polymer is not linear but rather a looped ellipsoid.

Furthermore the mechanical properties [64,65] of chromosomes in metaphase depend on the loops. Specifically the local stiffness and hence the flexibility [66] is determined by the loops.

6. Conclusion

An important finding concerning the three-dimensional architecture of eukaryotic genomes is that individual chromosomes are compartmentalized into loops [18] and topological domains [5–7,51], both of which depicting fundamental regulatory and structural building blocks of chromosomes that are stable between cell types. Chromatin interactions almost exclusively take place within topological domains and not across them.

Though the existence of this intra-chromosomal compartmentalization is proposed in all newly published results of 3C-like experiments, explanations from a theoretical point of view are scarce. In this review, we focused on the modeling of the experimental findings of both loop domains and topological domains, which, as opposed to the former, do not involve a closure to a loop. Loop domains can be readily simulated by statically adjusting the topology. Topological domains, on the other side, are characterized by a highly dynamic internal organization and can be modeled by assuming dynamic loop interactions accounting for this highly flexible internal structure [51]. The idea of enhancer–promoter units overlapping with these spatial domains [14] supports such an idea. Compared to the model assuming the interactions within topological domains to be due to supercoiling, our model can also explain loop domains and dynamic loop formation due to interaction between enhancers and promoters. Nevertheless, supercoiling is likely to cause further compaction of loops. The SBS model assumes that proteins bind to the chromatin fiber causing loop formation. Although quite similar to our approach, this actually needs different binders for the explanation of topological domains. Moreover, we can adjust the strength of the decrease of the contact probability as a function of the separating genomic distance.

Similarly to the findings in eukaryotic genomes, a recent study mapping the structure of the Caulobacter crescentus chromosome hints that bacterial genomes are also compartmentalized into topological domains of increased contact probability [13]. While it is probable that these domains are comprised of supercoiled plectonemes into a bottlebrush-like fiber for the case of the Caulobacter chromosome, it is possible that for other bacteria, such as *E. coli*, similar domains could be established by loop-forming proteins [46].

7. Methods

In this study, we performed Monte-Carlo simulations using the Dynamic Loop (DL) polymer model [21] to generate chromosomal conformations. The DL model incorporates chromatin loops by using a dynamic looping mechanism of the model fiber. When two monomers come into physical proximity to each other by diffusional motion, a cross-link can be created between them with a certain probability p_{loop}, which we refer to as looping probability. In case the cross-link is formed, a lifetime drawn from a Poisson distribution with mean value τ is assigned to it. The cross-link dissolves again after this lifetime, and thus, the loop vanishes. By this dynamic mechanism, there is a constant association and dissociation of non-adjacent monomers, resulting in loop creation and dissolution. We confined this dynamic loop formation to certain regions along the polymer chain in order to model topological domains.

In contrast to this, the topology of the backbone of the polymer is fixed during the simulation. For the polymer chains we used the well-established bond fluctuation method [67,68]. In the simulations a monomer of the polymer chain is randomly selected and, if possible, randomly moved to one of its nearest neighbors on the lattice. Excluded volume interactions are taken into account by preventing a lattice site to be occupied by more than one monomer. When simulating N monomers we define one Monte-Carlo step (MCS) to correspond to N moves, i.e. on average each monomer is translated once during a MCS.

3C-based technologies, such as Hi-C, are experimental methods that can quantify the contact frequency between different sites of the DNA molecule. Fortunately, in our simulations the contact frequency can be measured comparatively simple since we know the exact configuration of our polymer, i.e. the position of each single monomer in the three-dimensional space at each point in time. We only have to quantify the contact frequency of all pairs of monomers. By averaging over the whole ensemble of conformations and subsequent normalization we can make the step from contact frequency to contact probability p_c.

In order to generate thermodynamically equilibrated polymer conformations we used the Metropolis Monte Carlo method. Since subsequently created conformations are highly correlated, we determine, for each set of parameters, the autocorrelation function of the squared radius of gyration. Then, the integrated autocorrelation time τ_{int} is computed by applying the windowing procedure introduced by Sokal [69]. We consider two subsequent conformations as uncorrelated after $5\tau_{int}$ MCS therewith creating 10000—100000 independent configurations.

Further details on the simulations can be found in previous works [21,55].

Acknowledgments

We would like to thank Remus T. Dame, Frédéric Crémazy and Lei Liu for the stimulating and fruitful discussions. A.H. gratefully acknowledges funding by the Friedrich Naumann Foundation (FNF). This work was supported by a Grant from the International Human Frontier Science Program Organization (RGP0014/2014). Computer simulations were performed on the bwGRiD parallel computing facilities (http://www.bw-grid.de), member of the German D-Grid initiative, funded by the Ministry for Education and Research (Bundesministerium für Bildung und Forschung) as well as the Ministry for Science, Research and Arts Baden-Württemberg (Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg).

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